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Tolerability of Fluticasone Furoate/Vilanterol Combination Therapy in Children Aged 5 to 11 Years With Persistent Asthma

Amanda Oliver, MBBS, MRCP, FFPM[1]; Sandi VanBuren, RN[2]; Ann Allen, BSc (Hons)[3]; Melanie Hamilton, BSc (Hons)[4]; Lee Tombs, MSc[5]; Amir Inamdar, MBBS[1,*]; and Rodger Kempsford, PhD[3]

[1]*GlaxoSmithKline, Uxbridge, United Kingdom;* [2]*GlaxoSmithKline, King of Prussia, Pennsylvania;* [3]*GlaxoSmithKline, Stevenage, United Kingdom;* [4]*GlaxoSmithKline, Ware, United Kingdom; and* [5]*Synergy, Slough, United Kingdom*

ABSTRACT

Background: Asthma is a chronic disease afflicting millions of children worldwide. Short-acting β_2-agonist reliever medications and inhaled corticosteroid (ICS) maintenance therapies are effective treatments; however, many children remain uncontrolled with short-acting β_2-agonist and ICS treatment, in which case guidelines recommend adding a long-acting β_2-agonist.

Objective: We sought to investigate the safety profile, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) properties of the long-acting β_2-agonist vilanterol (VI) combined with the ICS fluticasone furoate (FF) administered via the ELLIPTA dry powder inhaler (GlaxoSmithKline, London, United Kingdom) in children aged 5 to 11 years with persistent asthma.

Methods: In this randomized, double-blind, repeated-dose, 2-way crossover study, data from 8- to 11-year-old children with asthma were reviewed before those from 5- to 7-year-old children with asthma. Patients received once-daily FF/VI, 100/25 μg, or FF, 100 μg, in the morning for 14 days, followed by a ≥7-day washout period before switching to the other treatment for 14 days; the study duration was ≤11 weeks. Primary end points were adverse events (AEs), clinical laboratory measurements, peak expiratory flow, maximum heart rate, blood pressure, and electrocardiographic parameters. Secondary end points comprised PK ($AUC_{0–4}$, C_{max}) and PD (serum potassium [0–4 hours], serum cortisol [0–12 hours], and glucose [0–4 hours]) parameters on day 14.

Results: Twenty-six children were randomized (58% boys; mean age, 8.1 years). No clinically significant changes in the primary end points were observed. Five patients reported 4 and 2 AEs with FF/VI and FF therapy, respectively. After FF/VI or FF treatment, the geometric mean ratios (90% CIs) for FF $AUC_{0–4}$ (1.02 [0.86–1.22]) and FF C_{max} (0.98 [0.65–1.48]) were similar. For serum glucose (0–4 hours) concentration, a difference of 0.50 mM (95% CI, 0.19–0.82 mM) was observed for FF/VI versus FF; no differences were observed for other PD parameters. No AEs were judged to be serious or treatment related. The PK profile of FF did not seem to be altered by VI and was not affected by age or sex. The significance of an increased serum glucose level is difficult to judge as measurements were taken from nonfasted patients. Results can be compared only with active treatment, and the ability to generalize is limited by the small number of patients in this single-center study.

Conclusions: Once-daily repeated dosing of FF/VI, 100/25 μg, using the ELLIPTA dry powder inhaler was as well tolerated as FF, 100 μg, in this small, selected population of 5- to 11-year-old, mostly white/caucasian children with persistent asthma. (*Clin Ther*. 2014;36:928–939) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: ICS, LABA, pediatric, pharmacodynamics, pharmacokinetics, tolerability.

*Current affiliation: Takeda Development Centre Europe Ltd, London, United Kingdom.

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INTRODUCTION

Asthma continues to be a major chronic disease in children.[1,2] Initially, short-acting β_2-agonist (SABA) rescue medication can alleviate symptoms as needed and maintain asthma control. Loss of asthma control is associated with more frequent use of rescue medication, increased symptoms, increased exacerbation frequency or severity, and reduced lung function.[2–4] If control is not maintained with SABA use, maintenance therapy is initiated with a low-dose inhaled corticosteroid (ICS).[2] Many pediatric asthmatic patients remain uncontrolled despite the addition of ICS therapy.[5,6] In children aged ≥ 5 years with asthma uncontrolled by SABA and low-dose ICS treatment, the addition of a long-acting β_2-agonist (LABA) is recommended[2] and provides the best overall control compared with alternatives such as increasing the ICS dose and adding a leukotriene receptor antagonist.[7]

In children, ICSs and ICSs/LABAs are typically dosed twice daily. The ICS fluticasone furoate (FF) is in development as once-daily monotherapy and together with the LABA vilanterol (VI) is an ICS/LABA combination therapy for adults and adolescents with asthma. Once-daily dosing can improve adherence in asthmatic patients,[8–10] which would be beneficial in pediatric patients, where adherence is known to be low[11]; FF[12–14] and VI[15] have demonstrated efficacy and tolerability with once-daily dosing in asthmatic patients aged ≥ 12 years and are being investigated in a dedicated pediatric development program. The safety profiles and pharmacokinetic (PK) and pharmacodynamic (PD) properties of FF[16] and VI[17] monotherapy have been investigated in crossover placebo-controlled studies.

This study sought to assess the safety profile of FF/VI therapy versus that of FF monotherapy and to determine whether the administration of FF combined with VI via the ELLIPTA dry powder inhaler (DPI) (GlaxoSmithKline, London, United Kingdom) affected the PK or PD properties of FF.

METHODS

Study Population

Boys and girls (premenarchal) aged 5 to 11 years diagnosed as having asthma ≥ 6 months before screening and weighing ≥ 20 kg were enrolled. The inclusion criteria were controlled asthma (Childhood Asthma Control Test score of >19[18] and peak expiratory flow rate [PEFR] $\geq 75\%$ of predicted); ≥ 4 weeks of stable asthma treatment with an ICS (fluticasone propionate, ≤ 400 μg daily, or an equivalent) and a SABA; and no significant medical conditions other than eczema or rhinitis. The exclusion criteria included the use of theophyllines, LABAs, or oral β_2-agonists; alteration of asthma therapy within 4 weeks; a history of life-threatening asthma; exacerbations requiring treatment with systemic corticosteroids or emergency department attendance (within 3 months); hospitalization (within 6 months); and visual evidence of oral candidiasis at screening. This study was approved by local ethics review committees (Quorum Review IRB, Seattle, Washington) and was conducted in compliance with Good Clinical Practice guidelines,[19] the Declaration of Helsinki,[20] and GlaxoSmithKline Standard Operating Procedures for all processes involved. Written informed consent was provided by a parent/guardian for each patient and was accompanied by informed assent from participants aged 7 to 11 years.

Study Design

This was a randomized, double-blind, repeated-dose, 2-period, crossover, Phase IIa study. Screening was within 28 days prior to dosing. Patients were separated into 2 cohorts: cohort I included those aged 8 to 11 years, and cohort II included those aged 5 to 7 years. Per the study protocol, dosing of cohort II occurred only after analysis of blinded tolerability and PK data from ≥ 6 patients in cohort I.

Patients were randomized and stratified by age (with ≥ 1 patient in each age group) to receive FF/VI, 100/25 μg, followed by FF, 100 μg, or FF, 100 μg, followed by FF/VI, 100/25 μg. The treatment periods were 14 days, separated by a washout period of ≥ 7 days, which was not formally capped. The planned total study length was ≤ 11 weeks, including screening and follow-up. Four patients exceeded the study duration (2×78 days, 1×84 days, and 1×98 days), but this was not judged to have affected the study outcome. Patients were dosed in the morning at the clinic on day 1, and tolerability assessments were performed up to 2 hours postdose. Patients self-dosed at home under parent/guardian supervision on days 2 to 13 within 1 hour of the original dose time. Parents/guardians were contacted on days 3, 7, and 10 to review dosing times, report adverse events (AEs), and deal with questions. Patients visited the clinic on day 14, were dosed within 1 hour of the original dose time, and were assessed on tolerability and PK and PD

parameters up to 12 hours postdose. All the treatments were delivered via the ELLIPTA DPI. Day 14 assessments were performed on day 15 if scheduling was an issue. Follow-up visits were within 7 to 14 days of the final dose. Patients continued taking their existing asthma medications during the run-in, washout, and run-out periods but abstained during the treatment periods. A SABA, salbutamol, was provided for as-needed symptomatic relief.

Tolerability Assessments

The AEs and serious AEs were recorded until the end of follow-up and were classified as mild, moderate, or severe in intensity. The PEFR measurements were recorded in triplicate at screening, predose, and postdose on days 1 (up to 2 hours) and 14 (up to 12 hours); predose at home on days 2 to 13 (study diary card); and during follow-up. Clinical laboratory values (hematology, chemistry, and urinalysis), vital signs (systolic and diastolic blood pressure and heart rate [HR]), and 12-lead electrocardiograms (ECGs) (QT corrected using the Fridericia correction [QTcF]) were also assessed; all the clinical laboratory data were analyzed at Quest Diagnostics (Valencia, California). The ECG measurements were recorded at screening, on day 1 predose and up to 2 hours postdose, on day 14 predose and up to 8 hours postdose, and during the follow-up visit; results were assessed by Quintiles (Mumbai, India). Blood samples were taken on day 14 predose and up to 4 hours (PK parameters, potassium, and glucose) or 12 hours (cortisol) postdose; all the PK samples were assessed at GlaxoSmithKline (Ware, United Kingdom). All the clinically significant changes from baseline were followed until resolution or stabilization.

PK Assessments

Blood samples were collected predose and up to 4 hours postdose on day 14 of each treatment period via an indwelling catheter. Samples were centrifuged at 1500*g* for 10 minutes. Plasma samples (150-mL aliquots) were analyzed for FF after treatment with FF/VI, 100/25 μg, or FF, 100 μg, by solid phase extraction using [^{13}C ^{2}H$_3$]-GW685698 as internal standard, followed by high-performance liquid chromatography with mass spectrometry detection using a TurboIonSpray interface and multiple reaction monitoring using an ABI API 5000 machine (Applied Biosystems, Waltham, Massachusetts). A gradient system using 5 mM of ammonium formate and methanol was run with column ACE 50 × 2.1 mm, C18 3 μm (Hichrom Ltd, Berkshire, United Kingdom) running at 45ºC. The ion transition for FF was m/z 539 to 313. The validation range of the assay was 10 to 1000 pg/mL for FF, and within-run precision, between-run precision, and bias were all $<12\%$. The lower limit of quantification for FF was 10 pg/mL.

Plasma samples (200-mL aliquots) were analyzed for VI after treatment with FF/VI, 100/25 μg, by solid phase extraction using ([^{2}H$_{12}$]-GW642444 as internal standard), followed by high-performance liquid chromatography with tandem mass spectrometry using an ABI API 5000 machine. A gradient system using 10 mM of ammonium formate containing 0.1% formic acid and acetonitrile containing 0.1% formic acid was run with column 50 × 2.1 mm i.d. Hypersil Gold 3 μm (Thermo Scientific, Loughborough, United Kingdom) running at 50ºC. The ion transition for VI was m/z 486 to 159. The validation range of the assay was 10 to 1000 pg/mL for VI, and within-run precision, between-run precision, and bias were all $\leq 10\%$. The lower limit of quantification for VI was 10 pg/mL.

Quality controls prepared at 3 different concentrations were analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. Quality control results from this study met the acceptance criteria of no more than one third of the quality control results deviating from the nominal concentration by $>15\%$, with ≥ 1 quality control result acceptable at each concentration.

The PK analyses of plasma concentration–time data were conducted using noncompartmental Model 200 of WinNonlin Professional software, version 5.2 (Pharsight Corp, St Louis, Missouri). The following parameters were derived: C_{max}, t_{max}, and AUC_{0-t}. The time of last quantifiable plasma concentration (t) was also reported.

PD Assessments

Blood samples were taken on day 14 via an indwelling catheter; serum cortisol determination samples were taken predose and then 2, 4, 8, and 12 hours after dosing. Samples for glucose and potassium analysis were collected predose and 10 min and 30 minutes and 1, 2, and 4 hours postdose. All the PD samples were analyzed by Quest Diagnostics. For analysis of serum cortisol levels, the high-throughput liquid

chromatography system was used to eliminate unwanted sample components. The detection was performed by the tandem mass spectrometer. The enzymatic method of analysis for glucose samples was based on the catalytic action of hexokinase on glucose and adenosine triphosphate to yield glucose-6-phosphate.[21] The glucose-6-phosphate is then reacted on by glucose-6-phosphate dehydrogenase with simultaneous reduction of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide hydride. The absorbance of the reduced nicotinamide adenine dinucleotide hydride, which is produced in an amount equimolar to the concentration of glucose, is read bichromatically at 340/380 nm. The absorbance value is then compared with the absorbance produced by a known calibrator. The result is then printed out directly in milligrams per deciliter . Serum potassium levels were measured by using a flow cell with an ion-selective electrode.[22] A statistical analysis was performed on the weighted mean potassium (0–4 hours) and weighted mean glucose levels (0–4 hours) on day 14. All the available derived values were used. A mixed-effects model was fitted with treatment and period as fixed effects and patient as a random effect. From these analyses, the difference between the adjusted means and corresponding 2-sided 95% CIs for FF/VI relative to FF was estimated.

The HR assessments were made on day 1 predose and 20 minutes and 1 and 2 hours postdose and on day 14 predose and 20 minutes and 1, 2, 4, and 8 hours postdose. The mean treatment differences on days 1 and 14, and their associated 95% CIs, were constructed.

Exploratory Pharyngometry and Inhalation Profile Assessments

Pharyngometry and inhalation profiles were collected at screening and predose on days 1 and 14 of each treatment period. Mouth and throat geometry was measured using acoustic reflectance (Eccovision; Sleep Group Solutions, North Miami Beach, Florida). Inhalation profiles were measured using an instrumented blinding box connected to an inhalation profile recorder (GlaxoSmithKline, Ware, United Kingdom). Attributes of FF/VI or FF dose emission from the ELLIPTA DPI were modeled through replication of selected inhalation profiles using an in vitro simulation method (Electronic Lung [eLung]; GlaxoSmithKline, Ware, United Kingdom)[23] and an anatomical throat cast. Predictions for the total emitted dose, ex-throat dose, and mass of ex-throat dose of particles <2 μm were made for each patient.

Statistical Methods

The primary end points comprised AEs, clinical laboratory measurements, PEFR (0–2 hours, day 1; 0–12 hours, day 14), systolic and diastolic blood pressure (0–8 hours, day 14), maximum HR (0–2 hours, days 1 and 14), and ECG parameters, including QTcF (0–2 hours, days 1 and 14). The secondary end points included PK parameters and serum cortisol (0–12 hours, day 14), potassium (0–4 hours, day 14), and glucose (0–4 hours, day 14) weighted mean levels.

Twenty-six patients were randomized to ensure that ≥ 20 patients completed the study, including ≥ 1 child from each age group. No formal sample size calculation was performed because no formal hypotheses were tested; sample size was based on feasibility. If no AEs of major concern were observed after dosing in 20 patients, then the calculated probability of the true rate of AEs of major concern in the whole population of patients, based on the upper 95% CI for the number of patients, would be less than 14%.

For maximum HR and QTcF (0–2 hours), differences between the 2 treatments were investigated using mixed-effects repeated-measures models. Treatment, period, day, and treatment × day interaction were fitted as fixed effects, and patient was treated as a random effect. The difference between the adjusted means and corresponding 2-sided 95% CIs for FF/VI relative to FF was estimated for days 1 and 14. Similarly, each of the 0- to 4-hour weighted mean potassium and glucose end points on day 14 were statistically analyzed using a mixed-effects model. Treatment and period were fitted as fixed effects and patient as a random effect. Serum cortisol weighted mean level (0–12 hours) on day 14 was $\log_e$-transformed, and a mixed model was fitted with treatment and period as fixed effects and patient as a random effect. For the FF analyte, a mixed-effects model was fitted on the day 14 $\log_e$-transformed C_{max} and AUC_{0-4} with treatment and period as fixed effects and patient fitted as a random effect. The ratio and corresponding 2-sided 90% CI for FF/VI relative to FF was estimated.

RESULTS

Patient Disposition and Baseline Characteristics

Twenty-six patients were enrolled and randomized to treatment, and 23 completed the study (Figure 1). All ages between 5 and 11 years were represented in the study with an approximate sex balance, and most patients (84%) had mild asthma, ie, well controlled with low-dose ICS therapy (Global Initiative for Asthma step 2) (Table I).

The most frequently reported concomitant medication was inhaled fluticasone propionate for asthma, taken by 18 patients as permitted during the run-in, washout, and run-out periods. Seven patients took other concomitant medications for nonasthmatic conditions that were judged not to have compromised the safety profile or to have affected the outcome of the study.

Safety Profile and Tolerability Results

Six AEs were reported by 5 patients, and all resolved during the study; 4 AEs were reported with FF/VI, 100/25 μg, and 2 with FF, 100 μg (Table II). Events of bronchitis and streptococcal pharyngitis (both during FF/VI treatment) were of moderate intensity, and all other AEs were mild. No AEs were considered to be treatment related. There were no serious AEs or AEs leading to withdrawal or death.

No clinically significant changes in clinical laboratory values were observed with FF/VI or FF treatment, and the mean clinical laboratory values observed between the 2 therapies were similar. There was no evidence of a clinically relevant difference in change from baseline in HR, systolic or diastolic blood pressure, or ECG measures after 14 days of repeated dosing with either intervention. Mean PEFRs did not differ between treatments for predose and postdose measures on day 1 or 14, and no worsening of PEFR was observed up to 20 minutes postdose with either treatment (see Supplemental Table I in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.

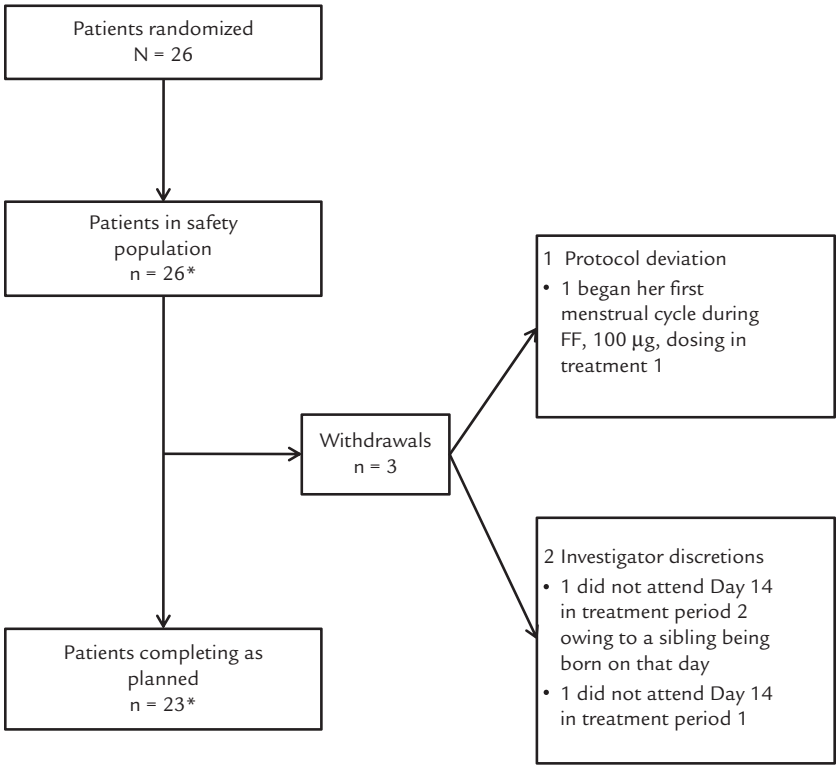

Figure 1. Patient disposition. *Cohort I (8–11 years old) comprised 15 patients, 12 of whom completed the study. Cohort II (5–7 years old) comprised 11 patients, all of whom completed the study. FF = fluticasone furoate.

Table I. Patient demographic characteristics.

Characteristic	Study Population (N = 26)
Age, y (mean [range])	8.1 (5–11)
Age, No.	
5 y	2
6 y	5
7 y	4
8 y	4
9 y	3
10 y	4
11 y	4
Female sex, No. (%)	11 (42)
Height, cm (mean [range])	131.8 (113–156)
Weight, kg (mean [range])	32.56 (20.0–71.8)
BMI, mean (range)	18.13 (14.0–29.5)
Race, No. (%)[*]	
White: caucasian/European heritage	21 (81)
African American/African heritage	3 (12)
White: Arabic/North African heritage	1 (4)
Mixed race: African American/African heritage and white	1 (4)
Asthma severity, No. (%)[†]	
Mild (well-controlled with GINA step 2 low-dose ICSs)	21 (84)
Moderate (well-controlled with GINA step 3 medium-dose ICSs)	4 (16)

BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid.

[*]Percentages do not sum to 100% due to rounding.

[†]n = 25. Disease severity was calculated by assessing the use of concomitant medications during the run-in and washout periods of the study, during which patients were to continue using the medications that they had used before screening. As a result, the disease severity of the patient who did not attend the clinic on day 14 of treatment period 1 (and was withdrawn as a result) is unknown.

03.014). No worsening of mean PEFR compared with baseline during the 14-day treatment period was seen for either treatment.

PK Results

Twenty-four patients were included in the FF PK analysis; 2 did not complete treatment with either FF/VI or FF and were not included. The FF concentrations were quantifiable in most patients for up to 4 hours after the final doses of FF/VI and FF on day 14 (Figure 2A). The FF concentrations were not quantifiable in 3 patients for FF/VI and in 5 for FF; these values were set to 0 in the analysis of results. The FF C_{max} and $AUC_{0–4}$ values were similar between the 2 treatments (Table III). Individual FF scatterplots of C_{max} or $AUC_{0–4}$ by age indicate no effect of age on these individual PK parameters (Figures 2B and 2C). The FF PK profile was similar after treatment with FF/VI or FF alone, with an adjusted mean ratio (90% CI) of 1.02 (0.86–1.22) for $AUC_{0–4}$, and 0.98 (0.65–1.48) for FF C_{max}.

Twenty-three patients were included in the VI PK analysis; 3 did not complete treatment with FF/VI and were not included. As with FF, VI concentrations were quantifiable in most patients up to 4 hours after the final dose of FF/VI on day 14 (Figure 3A); 2 patients had no quantifiable VI concentrations that were set to 0 in the analysis of results. The VI C_{max} was observed

Table II. Number of patients with any AEs.

AE	Patients, No. (%) (N = 25)	
	FF/VI, 100/25 µg*	FF, 100 µg†
Any AE	4 (16)	1 (4)
Headache	1 (4)	0
Upper respiratory tract infection	0	1 (4)
Conjunctivitis	1 (4)	0
Conjunctivitis viral	0	1 (4)
Bronchitis	1 (4)	0
Streptococcal pharyngitis	1 (4)	0

AE = adverse event; FF = fluticasone furoate; VI = vilanterol.
*One patient received FF, 100 µg, but was withdrawn (investigator discretion) before receiving FF/VI, 100/25 µg, and was not included in the FF/VI, 100/25 µg, safety analysis.
†One patient received FF/VI but was withdrawn (protocol deviation) before receiving FF, 100 µg, and was not included in the FF, 100 µg, safety analysis.

a median of 10 minutes after the administration of FF/VI (Table III). Individual scatterplots of VI C_{max} and $AUC_{0–4}$ by age indicate no clear effect of age on these individual PK parameters (Figures 3B and 3C).

PD Results

No clinically significant differences were observed in maximum HR and QTcF (0–2 hours) on day 1 or day 14 between the 2 treatments (Figures 4A and 4B; see Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.03.014). Weighted mean serum potassium and cortisol levels, measured at 0 to 4 hours and 0 to 12 hours, respectively, were not significantly clinically different between the 2 treatments on day 14 (Figures 4C and 4D; see Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.03.014). Weighted mean serum glucose levels, assessed over 0 to 4 hours on day 14, were slightly higher after FF/VI than after FF, with an average difference of 0.50 mM (95% CI, 0.19– 0.82 mM) (Figure 4E; see

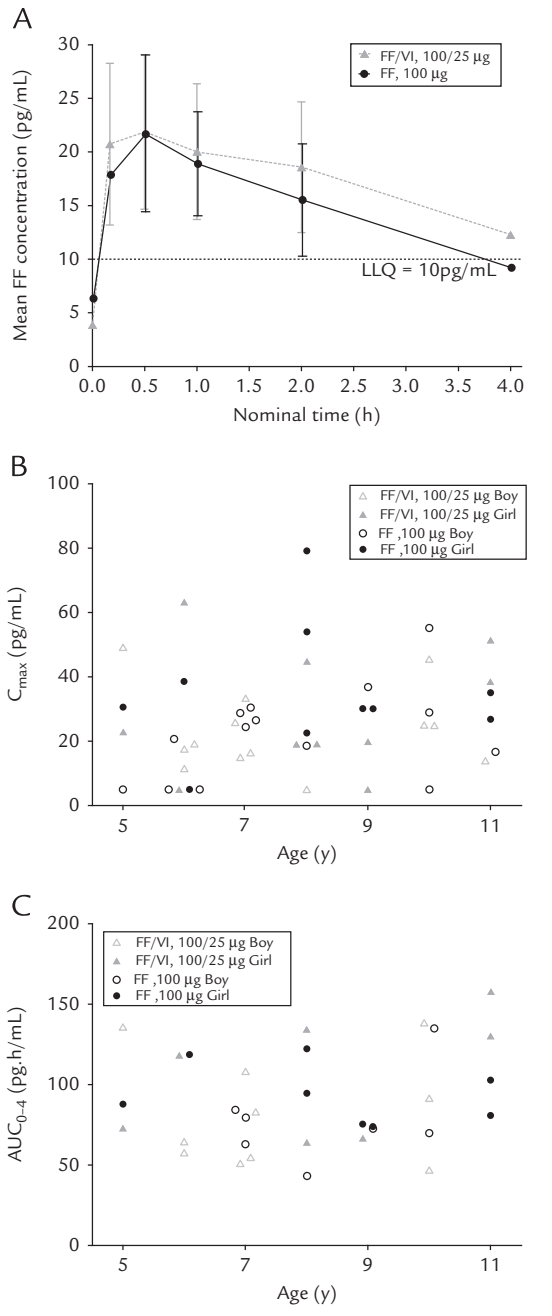

Figure 2. (A) Mean (95% CI) fluticasone furoate (FF) concentration-time profiles after once-daily dosing of FF/vilanterol (VI), 100/25 µg, or FF, 100 µg for 14 days. (B) Scatterplot of day 14 individual FF C_{max} values by age for FF/VI, 100/25 µg, and FF, 100 µg. (C) Scatterplot of day 14 individual FF $AUC_{0–4}$ values by age for FF/VI, 100/25 µg, and FF, 100 µg. LLQ = lower limit of quantification.

Table III. Summary of FF and VI PK parameters.

Parameter	FF/VI, 100/25 μg, FF Measured (n = 24)	FF, 100 μg, FF Measured (n = 24)	FF/VI, 100/25 μg, VI Measured (n = 23)	Ratio of Adjusted Geometric Means for FF (90% CI), FF/VI, 100/25 μg/FF, 100 μg
AUC_{0-4}, pg.h/mL*	86.1 (70.0–106.0)	83.8 (71.5–98.3)	119.2 (102.4–138.7)	1.02 (0.86–1.22)
C_{max}, g/mL*	20.7 (15.2–28.4)	21.2 (14.9–30.0)	44.2 (27.7–70.7)	0.98 (0.65–1.48)
t_{max}, h†	0.97 (0.00–2.07)	0.50 (0.00–3.95)	0.17 (0.00–2.08)	

FF = fluticasone furoate; PK = pharmacokinetic; VI = vilanterol.
*Geometric mean (95% CI).
†Median (range).

Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.03.014).

Exploratory Pharyngometry and Inhalation Profile Assessments

Pharyngometry data for 23 patients were available for assessment. The mean (SD) distance of assessment (lips to larynx), cross-sectional area, and oropharyngeal volume were 19.26 (0.72) cm, 3.76 (2.20) cm^2, and 72.35 (42.44) cm^3, respectively, on day 14 of the FF/VI treatment period and 19.10 (1.00) cm, 3.70 (2.28) cm^2, and 71.47 (45.84) cm^3 on day 14 of the FF treatment period. Pressure drop versus time profiles recorded while inhaling across the resistance of the DPI resulted in an overall mean (SD) peak inspiratory flow rate (PIFR) for day 14 of 67.4 (16.4) L/min and 64.8 (15.9) L/min for the FF/VI and FF treatment periods, respectively. No relationship was seen between PIFR and body mass index, and a weak trend was observed for a relationship between PIFR and patient age or height (data not shown). Through use of the eLung in vitro simulation method, dose emission attributes of FF and VI delivered via the ELLIPTA DPI as FF/VI or FF alone were predicted for each patient. For day 14 data, the mean total emitted dose, mean ex-throat dose, and mean predicted mass of particles <2 μm, respectively, were predicted to be 87.6, 25.0, and 6.7 μg for FF when delivered as FF/VI; 20.3, 8.5, and 4.9 μg for VI when delivered as FF/VI; and 86.3, 24.3, and 6.0 μg for FF when delivered as FF alone.

DISCUSSION

The results of this study suggest that an inhaled fixed-dose combination of FF/VI, 100/25 μg, exhibits a similar tolerability profile as FF, 100 μg, in pediatric patients aged 5 to 11 years with persistent asthma. Treatment with FF/VI did not give rise to clinically significant PD effects, and the PK profile of FF was similar when dosed alone or combined with VI, suggesting that simultaneous administration of FF/VI via the ELLIPTA DPI had no adverse effect on the PK profile of FF in children.

Although more AEs were reported during FF/VI treatment (n = 4) than during FF monotherapy (n = 2), none were serious, and the incidence was low. Most AEs were described as mild in intensity, and all were typical childhood illnesses (bronchitis, conjunctivitis, headache, streptococcal pharyngitis, and upper

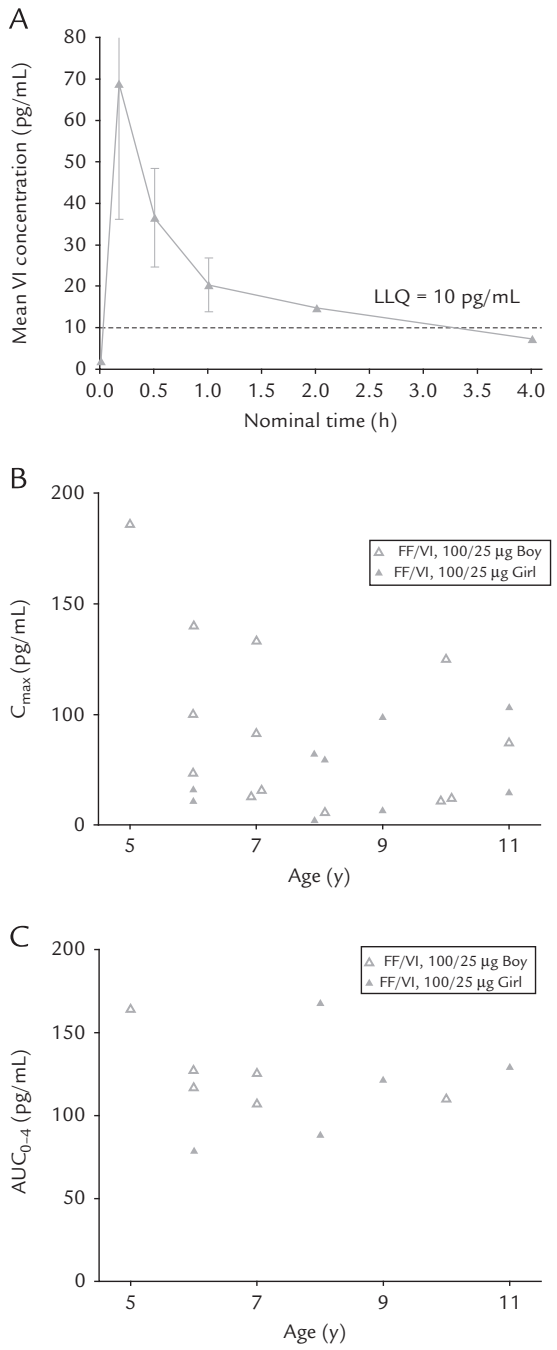

Figure 3. (A) Mean (95% CI) concentration-time profile after once-daily dosing of fluticasone furoate (FF)/vilanterol (VI) for 14 days. (B) Scatterplot of day 14 individual VI C_{max} values by age. (C) Scatterplot of day 14 individual VI AUC_{0-4} values by age. LLQ = lower limit of quantification.

respiratory tract infection); none were judged to be drug related. Because of the small number of patients and AEs, it was not possible to make definitive deductions regarding rates of AEs. No pattern was observed indicating a difference in AEs between the 2 treatments.

A variety of systemic PD effects have been associated with high-dose LABA and high-dose ICS therapy. Use of LABAs has been associated with increased HR, QTcF, and serum glucose levels and decreased blood potassium levels,[24] whereas ICS therapy has been associated with decreased serum cortisol levels and growth retardation in children.[25] We observed no differences of clinical importance after FF/VI therapy versus FF monotherapy in HR, QTcF, serum potassium levels, or serum cortisol levels. A small increase in weighted mean serum glucose levels (0–4 hours) of 0.5 mM was observed on day 14 with FF/VI therapy compared with FF therapy. It is difficult to judge the clinical significance of this finding because the effect of food intake on glucose levels was not controlled, and the samples were taken from children in a nonfasted state. It was observed that owing to the length of the first clinic visit, parents fed their children before and during subsequent visits, which may explain some of the variation. Treatment with FF/VI did not induce any clinically significant changes in glucose levels in nonfasted adults in a recent study of FF/VI versus fluticasone propionate,[26] and in a study of VI, 25 µg, in pediatric asthmatic patients, no difference was observed in serum glucose levels compared with placebo.[17]

In this study, the PK profile of FF did not differ markedly for AUC_{0-4} or C_{max} values whether dosed as monotherapy or as FF/VI, which is consistent with data previously obtained in adults at higher doses.[27,28] Furthermore, the PK profiles of FF and VI did not seem to be affected by age or sex. Because VI was administered only as FF/VI in this study, the effects of FF on the PK profile of VI cannot be readily determined, although no interaction has been seen in adults.[27,28] The small difference in C_{max} for VI, which was 44.2 pg/mL after 14 days of FF/VI therapy in the present study compared with 97.4 pg/mL after 7 days of VI monotherapy in a previous pediatric study,[17] is likely to reflect interstudy variability because of the small number of patients. The t_{max} was comparable between the 2 studies (12 minutes in the monotherapy study and 10 minutes in the present study), suggesting

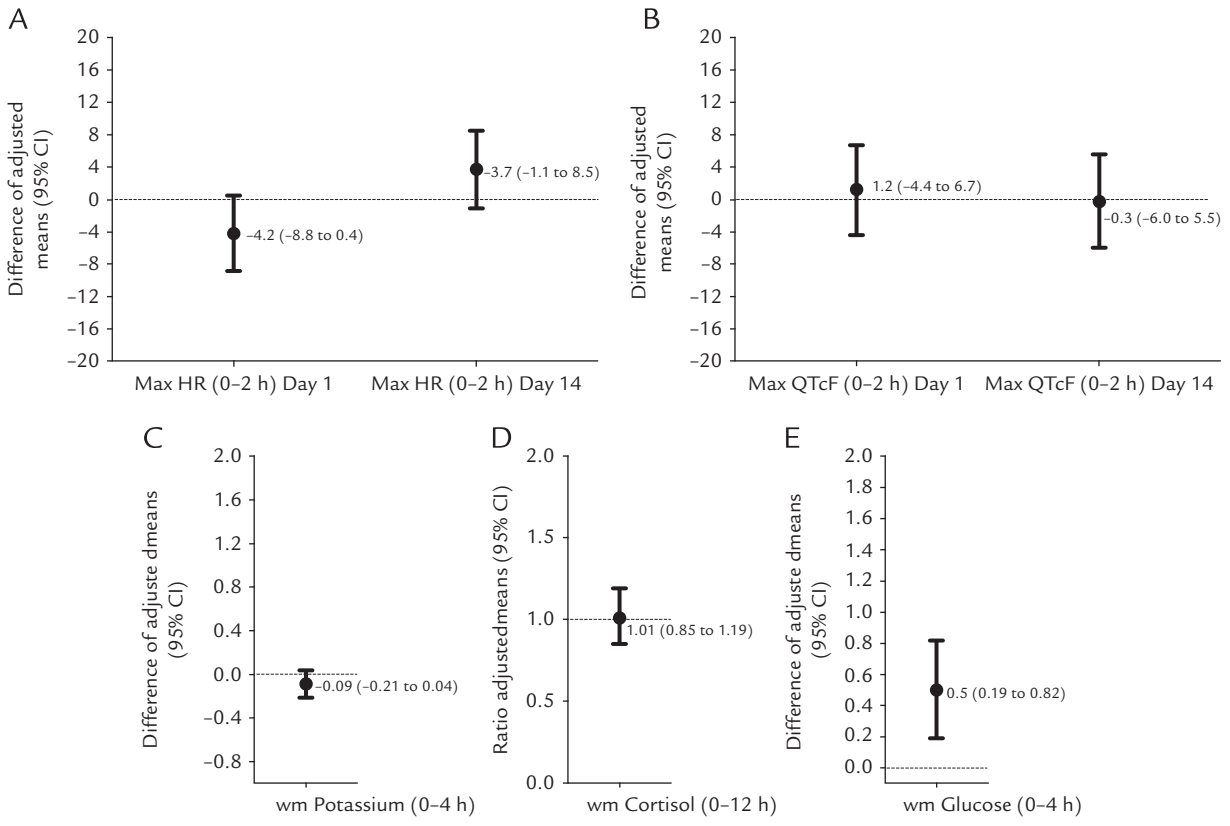

Figure 4. Difference between the 2 treatments (fluticasone furoate [FF]/vilanterol [VI], 100/25 μg – FF, 100 μg) in (A) maximum (max) heart rate (HR) (bpm), 0 to 2 hours, days 1 and 14; (B) max QT corrected using the Fridericia correction (QTcF) (msec), 0 to 2 hours, days 1 and 14; (C) weighted mean (wm) serum potassium levels (mM), 0 to 4 hours, day 14; (D) wm serum cortisol levels (mM), 0 to 12 hours, day 14; and (E) wm serum glucose levels (mM), 0 to 4 hours, day 14.

that FF therapy does not affect VI absorption, similar to the lack of interaction seen in adults.[27] The PEFR measurements, included for investigation of the safety profile and tolerability and not for efficacy, were similar between the 2 treatments.

This study benefited from a crossover design in which patients acted as their own controls; a good sex balance was achieved, and each age between 5 and 11 years was represented by ≥1 patient. The low withdrawal rate (3 of 26 patients) and the collection of serial blood samples over a 4-hour period for PK analysis and a 12-hour period for PD analysis allowed for adequate assessment of these end points. This study was conducted in well-controlled asthmatic patients receiving a stable regimen of low or medium doses of ICS in a single center in 1 country, ensuring consistency in standard of care between patients but limiting generalizability. The limitations of this study include the lack of a placebo control arm, which was omitted to minimize the risk of patients developing uncontrolled asthma. This limits interpretation of the results to the effects of active therapy only; however, in previous placebo-controlled trials in pediatric patients, the safety profiles of FF[16] and VI[17] did not differ markedly from that of placebo, and the safety profiles of FF/VI and FF in this study are similar to those observed in the placebo-controlled studies. In addition, because this study was not designed as a noninferiority study, the results can be interpreted only in a descriptive manner. Long-term tolerability and safety issues could not be addressed in this study owing to the

short length of the treatment period and because the small population size was not large enough to identify any potential rare effects.

CONCLUSIONS

Once-daily dosing of FF/VI, 100/25 μg, for 14 days seemed to be tolerated as well as FF, 100 μg, in children aged 5 to 11 years with persistent asthma. Systemic exposure to FF was similar in patients after the administration of FF/VI or FF, and there was no apparent relationship between the age of the patient and FF or VI C_{max} and AUC values. In this small and nonfasted study, serum glucose levels were slightly higher in patients after treatment with FF/VI compared with FF; however, no other clinically significant PD effects associated with ICS or LABA treatment were observed in this study. Data collected from the eLung suggest that the PIFR achieved by 5- to 11-year-olds with persistent asthma when inhaling through the ELLIPTA DPI was sufficient to predict consistent product performance. Once-daily FF/VI, 100/25 μg, and FF, 100 μg, delivered via the ELLIPTA DPI are, therefore, potential therapeutic options for the treatment of children aged 5 to 11 years with persistent asthma.

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All the authors provided input into the design and/or interpretation of the study and the writing of the manuscript. Ms. Allen conducted the pharmacokinetic analysis, and Mr. Tombs conducted the statistical analysis.

CONFLICTS OF INTEREST

Ms. Oliver, Ms. VanBuren, Ms. Allen, Ms. Hamilton, and Dr. Kempsford are employees of GlaxoSmithKline (the sponsor of the study). Mr L. Tombs is a consultant for Synergy, and Mr. Inamdar was an employee of GlaxoSmithKline when the study was conducted and is currently a shareholder of GlaxoSmithKline and an employee of Takeda Development Centre Europe Ltd. Employees of the sponsor were involved in the conception, design, and conduct of the study, and in data collection and analysis. All authors, including authors employed by the sponsor, participated in the development of the manuscript, and had access to the data from the study. The decision to submit for publication was that of the authors alone. The sponsor provided funding for editorial support and payment of the journal page and open-access fees. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.03.014.

REFERENCES

1. Fuhlbrigge AL, Adams RJ, Guilbert TW, et al. The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines. *Am J Respir Crit Care Med*. 2002;166:1044–1049.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention: updated 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf. Accessed January 30, 2014.
3. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000;343:1054–1063.
4. Sorkness CA, Lemanske RF Jr, Mauger DT, et al, for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol*. 2007;119:64–72.
5. Liu AH, Gilsenan AW, Stanford RH, et al. Status of asthma control in pediatric primary care: results from the pediatric Asthma Control Characteristics and Prevalence Survey Study (ACCESS). *J Pediatr*. 2010;157:276–281.
6. Szefler SJ. Advances in pediatric asthma in 2009: gaining control of childhood asthma. *J Allergy Clin Immunol*. 2010;125:69–78.
7. Lemanske RF Jr, Mauger DT, Sorkness CA, et al, for the Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010;362:975–985.
8. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J*. 2005;14:88–98.

9. Price D, Robertson A, Bullen K, et al. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med*. 2010;10:1.
10. Cochrane GM, Horne R, Chanez P. Compliance in asthma. *Respir Med*. 1999;93:763–769.
11. McQuaid EL, Everhart RS, Seifer R, et al. Medication adherence among Latino and non-Latino white children with asthma. *Pediatrics*. 2012; 196:e1404–e1410.
12. Bateman ED, Bleecker ER, Lötvall J, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. *Respir Med*. 2012;106:642–650.
13. Bleecker ER, Bateman ED, Busse WW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2012;109:353–358.
14. Busse WW, Bleecker ER, Bateman ED, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax*. 2012;67:35–41.
15. Lötvall J, Bateman ED, Bleecker ER, et al. 24h duration of the novel LABA vilanterol trifenatate in asthma patients treated with ICSs. *Eur Respir J*. 2012;40:570–579.
16. Oliver A, Allen A, VanBuren S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of fluticasone furoate, a novel inhaled corticosteroid, in children aged 5–11 years with persistent asthma: a randomized trial. *Clin Pharmacol Drug Dev*. 2013 Oct 21. [Epub ahead of print].
17. Oliver A, VanBuren S, Allen A, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of vilanterol, a novel inhaled long-acting ß-agonist, in children aged 5–11 years with persistent asthma: a randomized trial. *Clin Pharmacol Drug Dev*. 2014 Feb 6. [Epub ahead of print].
18. Juniper EF, Gruffydd-Jones K, Ward S, et al. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J*. 2010;36:1410–1416.
19. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: guidance for good clinical practice E6(R1): dated 10 June 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed January 4, 2014.
20. WMA General Assembly. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, Korea, October 2008. http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Updated October 2008. Accessed January 4, 2014.
21. Stein MW Determination with Hexokinase and Glucose-6-Phosphate Dehydrogenase. In: *Clinical Methods of Enzymatic Analysis*. Waltham, Mass: Academic Press; 1965: 117.
22. Tietz NW. *Fundamentals of Clinical Chemistry*. 3rd ed. Philadelphia, Pa: WB Saunders; 1987.
23. Burnell PKP, Malton A, Reavill K. Ball MHE. Design, validation and initial testing of the Electronic Lung™ device. *J Aerosol Sci*. 1998; 29:1011–1025.
24. Cazzola M, Page CP, Roglianai P, et al. β_2-Agonist therapy in lung disease. *Am J Respir Crit Care Med*. 2013;187:690–696.
25. Ahmet A, Kim H, Spier S. Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2011; 7:13.
26. Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β_2 agonist vilanterol administered once daily for 52 weeks in patients $\geq$12 years old with asthma: a randomised trial. *Thorax*. 2013;68: 513–520.
27. Kempsford R, Allen A, Bareille P, et al. The safety, tolerability, pharmacodynamics and pharmacokinetics of inhaled fluticasone furoate (FF) and vilanterol (VI) are unaffected by administration in combination. *Eur Respir J*. 2011;38:138s.
28. Nakahara N, Wakamatsu A, Kempsford R, et al. The safety, pharmacokinetics and pharmacodynamics of a combination of fluticasone furoate and vilanterol in healthy Japanese subjects. *Int J Clin Pharmacol Ther*. 2013;51:660–671.

Address correspondence to: Amanda Oliver, MBBS, MRCP, FFPM, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK. E-mail: Amanda.j.oliver@gsk.com

SUPPLEMENTAL MATERIAL

Supplemental Table I. Average clinic visit peak expiratory flow rate. Data are given as liters per minute.

		FF/VI, 100/25 μg (n = 25)		FF, 100 μg (n = 25)	
Day	Time Point	No.	Mean (95% CI)	No.	Mean (95% CI)
1	Baseline	25	219.0 (197.0–241.0)	25	223.6 (200.1–247.1)
	10 min	25	218.8 (196.9–240.7)	25	223.0 (200.2–245.8)
	20 min	25	222.4 (200.3–244.5)	25	228.2 (204.8–251.6)
	1 h	25	223.2 (200.8–245.6)	25	227.2 (204.9–249.5)
	2 h	25	227.0 (203.9–250.1)	25	228.6 (206.2–251.0)
14	Predose	23	224.8 (201.9–247.6)	24	215.0 (193.6–236.4)
	20 min	23	227.2 (204.6–249.7)	24	218.1 (196.1–240.1)
	2 h	23	235.7 (212.7–258.6)	24	225.8 (205.2–246.4)
	12 h	23	238.9 (214.8–263.1)	24	230.4 (208.2–252.6)

FF = fluticasone furoate; VI = vilanterol.

Supplemental Table II. Comparison of pharmacodynamic measures.

Measure	Comparison	Day	Adjusted Means Test – Reference	Difference of Adjusted Means (95% CI of Difference)
Heart rate, bpm	FF/VI, 100/25 μg – FF, 100 mcg	1	84.4 – 88.6	–4.2 (–8.8 to 0.4)
		14	89.4 – 85.7	3.7 (–1.1 to 8.5)
QTcF, msec	FF/VI, 100/25 μg – FF, 100 μg	1	403.3 – 402.2	1.2 (–4.4 to 6.7)
		14	404.0 – 404.2	–0.3 (–6.0 to 5.5)
Glucose, mML	FF/VI, 100/25 μg – FF, 100 μg	14	5.58 – 5.07	0.50 (0.19 to 0.82)
Potassium, mM	FF/VI, 100/25 μg – FF, 100 μg	14	4.06 – 4.15	–0.09 (–0.21 to 0.04)
Cortisol, mM*	FF/VI, 100/25 μg / FF, 100 μg	14	193.77/192.50	1.01 (0.85 to 1.19)

bpm = beats per minute; FF = fluticasone furoate; QTcF = QT corrected using the Fridericia correction; VI = vilanterol.
*Adjusted ratio.